Appendix F-2

Benzene White Paper

White Paper by Dr. Bernard Goldstein
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Abstract

Benzene is a known cause of aplastic anemia and of human leukemia. At community air pollution levels on which the benefits analysis for benzene control are to be based, there is no firm evidence to support a non-neoplastic effect. Estimation of the leukemic effect at such levels requires extrapolation across about three orders of magnitude of benzene dose. There is currently insufficient evidence to depart in any direction from low dose linearity.

Introduction

Benzene has been chosen as one of three compounds to be Case Studies for the **SAB/EPA Workshop on the Benefits of Reductions in Hazardous Air Pollutants: Developing Best Estimates of Dose-Response Functions.** The goal of the Workshop is to discuss dose response assessment methods for hazardous air pollutants (HAP) that are useful for assessing the benefits of emission control measures. This document is intended to provide a background for this discussion.

The literature on benzene toxicity is perhaps as large as that for any of the compounds designated as HAPs under the US Clean Air Act. This information has been extensively reviewed elsewhere (Caprino and Togna, 1998; Goldstein and Witz, 2000; Snyder et al, 1993; Smith and Fanning, 1997; Goldstein, 1977; Benzene '95 Conference, 1996; Krewski and Snyder, 2000). I will focus on those studies that may be particularly useful for providing the information needed for economic analysis of the benefits of reducing benzene exposure specifically related to the control of HAPs under the 1990 CAA Amendments. I have been asked to do this relatively late in the process. There has not been time to go through a detailed analysis of the basis for the different risk assessments for benzene, nor do I have the requisite expertise to clearly explicate the major differences in mathematical modeling approaches. Perhaps this is an advantage.

The organizers of the workshop have commissioned an "Economist's Perspective" by Lester Lave, a noted economist who has made major contributions to the economic analysis of air pollution health effects. This is not the place to respond to all of the issues raised by his very provocative piece which unfortunately demonstrates how poorly regulatory biological scientists have communicated with economists, even ones active in the field of risk assessment such as Dr Lave. However, it does lead to a recommendation.

To better understand the interface between regulatory risk assessment and economic benefit analysis, we should rephrase the benzene-related question being asked. The current question is how to estimate the benefit of partially reducing community benzene exposure now in the range of a few parts per billion. Instead, I suggest that EPA develop a hypothetical example of an economic analysis aimed at determining the benefits of reducing a putative workplace standard for benzene of 30 ppm, TWA to a level of perhaps 15 ppm, TWA. Thirty ppm is a useful baseline because it is in this range that there are data about actual leukemia risk and on non-cancer endpoints as well. A target of 15ppm is suggested because it represents only a two-fold reduction to a level that is still within the range of existing human and animal data. A two-fold reduction in outdoor benzene levels is also presumably a reasonable outcome of the new MACT strategy for benzene. The goal of this

exercise would be to obtain a better understanding of the biological uncertainties in the rich benzene data base which impact on a benefit analysis when there is no need for extrapolation to much lower exposure levels. Once this has been clarified, we can more readily address the extrapolation issues relevant to the perhaps three orders of magnitude lower levels of benzene exposure needed for HAPs benefit analysis.

An additional point about the history of HAP regulation relates to this Workshop. Two major driving forces for the 1990 CAA amended approach to regulate HAPs were impatience at the previous rate of EPA's regulatory approach and the impact of TRI data showing the many tons of unregulated pollutants being released into the air . Using a process which required an initial finding of likelihood of adverse effects, relatively few agents were previously regulated under Section 112 of the CAA. Benzene was one of them and in fact there is a clear statement of the use of risk assessment and of economic analysis in the 1984 benzene decision document (EPA, 1984). This included a table describing the costs and the number of leukemia deaths averted for each of the control approaches that were considered (Goldstein, 1985). Further, as only certain of these controls were then imposed, one could relatively easily reconstruct the risk benefit criteria underlying the decision.

In contrast, the present CAA lists more than 180 compounds to be regulated by EPA, in essence shifting the regulatory burden from the government which had to make an initial finding of likely adverse effects before listing, to industry who now must bring sufficient evidence that there are no adverse effects in order to delist. Congress moved away from risk assessment as the primary basis for regulation to a technology based approach in which risk considerations only come into play after Maximum Available Control Technology (MACT) has been instituted. For almost none of these previously unlisted compounds is there the rich data base available for benzene or for the other compounds previously chosen for listing under Section 112. Further, for many of the compounds for which there are ample human data, such as the alkyl benzenes, the data strongly suggest that no measurable adverse effects are likely at community exposure levels. Yet Congress clearly intended such compounds to be subject to MACT control irrespective of the lack of convincing data showing adverse effects. It is inconsistent and perhaps disingenuous of Congress to both disavow risk assessment as the primary basis for the regulatory control of HAPs while at the same time insisting that EPA use risk assessment as a means of demonstrating the benefit of the technology-based regulatory approach which it has imposed.

Health Effects of Benzene

Benzene has been known to produce destruction of the human bone marrow since the 19th Century. In humans, and in all laboratory animals tested, benzene produces a dose-dependent destruction of bone marrow precursor cells that are responsible for the production of mature red blood cells, platelets, and granulocytic and lymphocytic white blood cells. This is accompanied by chromosomal damage. The result is a decrease in all formed elements in the blood known as pancytopenia. A severe form of pancytopenia, aplastic anemia, includes marked loss of bone marrow cellularity and is a frequently fatal disorder.

Benzene is also a known human carcinogen, indisputably causing acute myelogenous leukemia and its variants (collectively called Acute Nonlymphocytic Leukemia - ANLL). It is also likely to cause other hematological tumors. An intermediate diagnosis between benzene induced pancytopenia and ANLL is myelodysplasia, a preleukemic condition characterized by morphological abnormalities and an increase in number of bone marrow precursors representing a monoclonal expansion. Both myelodysplasia and ANLL can occur without being preceded by clinically overt pancytopenia.

At concentrations well over 100 ppm (320 mg/m^3) benzene also causes central nervous system anesthetic-like effects common to alkyl benzenes and other VOCs. While an occupational hazard in enclosed spaces, this non-hematological effect is clearly not pertinent to considerations of HAP control and will not be discussed further. Based on relatively weak evidence in animal studies, more information on the potential for benzene-induced developmental effects in humans would be welcome, but again there seems to be no basis for considering such effects in the present document.

Benzene Exposure Levels Pertinent to Economic Analysis of the Impact of Control of HAPS

In order to provide a discussion of benzene toxicity pertinent to the purposes of this Workshop I have briefly and incompletely reviewed the literature concerning expected outdoor community concentrations of benzene. The focus is on the question of whether non-cancer hematological effects might occur. Accordingly, the goal is to pick a level that would represent a high community exposure that would be a reasonable target for assessing the health and economic impact of MACT control measures. For neoplastic endpoints, if one assumes a linear risk then the absolute level is not important – only the extent of reduction in benzene exposure and the size of the population is needed to calculate the number of leukemia cases averted. But for non-cancer effects the presumption of a no-effect level requires that some attempt be made to determine likely high community exposure levels.

Community outdoor benzene levels even in reasonably polluted areas appear to range well below 10 ppb (32 ：g/m^3). Wallace and his colleagues have measured outdoor air benzene concentrations in various parts of the United States as part of the Total Exposure Assessment Measurement (TEAM) study. In an overview of these studies the mean outdoor air benzene concentration based on backyard measurements of 175 homes in six urban areas was 6 ug/m^3 (Wallace, 1991). The highest levels in the TEAM study came from one of the two studies in Los Angeles where the outdoor air concentrations appeared to range up to 30 ug/m^3 with a geometric mean of 16 ug/m^3 (Wallace, 1986). In a relatively polluted area of New Jersey, the mean levels were 4.1 ug/m^3 at night and 3.8 ug/m^3 during the day. Lagrone (1989) reported outdoor benzene levels in a network of six sites located in an industrial area of Houston ranged from 1.4-5.8 ppb, mean 3.6 ppb, (4.5 - 18.6：g/m^3, mean 11.5 ：g/m^3) during the period September 1987 to March 1988. Johnson et al (1991) used a variety of models to estimate incremental ambient benzene concentrations to receptors living near seven bulk gasoline storage facilities in North Carolina. The highest modeled fenceline annual average benzene incremental concentration was 2.1 ppb (6.7：g/m^3). EPA reported that 1991 benzene concentrations in Lima, Ohio, ranged from 1.1 to 6.8 ug/m^3, mean 2.6 ug/m^3. EPA has also concluded that the background concentration of benzene, attributable to long range transport and non-anthropogenic sources, was 0.48 ug/m^3 (Woodruff et al, 1998). Data from 97 samples taken as

part of the NHEXAS study in EPA Region 5 shows a median benzene level of 2.9 ug/m^3 and a 90th percentile level of 5.6 ug/m^3 (Clayton et al, 1999). There appears to be good evidence that ambient benzene concentrations are decreasing. Based upon monitoring network data, the California Air Resources Board (CARB, 1997) has estimated a population-weighted annual concentration of 14.7 ug/m^3 benzene in 1982 and 2.3 ug/m^3 in 1996.

Benzene Toxicology

To a toxicologist benzene is both fascinating and frustrating. It is a well studied compound that has provided much insight into general toxicological mechanisms of action and is particularly relevant to understanding target organ toxicity related to the bone marrow. Its metabolism has also been thoroughly evaluated and, although complex, is reasonably well understood (Snyder and Hedli, 1996). We also know that it is one or more benzene metabolites, not benzene itself, that is responsible for its hematological toxicity. Yet the linkage between benzene metabolism and benzene hematotoxicity remains elusive. It is not at this time even certain that the toxicological mechanisms by which benzene destroys bone marrow precursor cells leading to aplastic anemia are the same mechanisms producing cancer of these cells. What we do know suggests that Occam's Razor is dull, that there is not a single benzene metabolite producing a single mechanism of cell damage and eventual mutation or cell death (Goldstein, 1990). Rather there are multiple metabolites producing effects in multiple biological pathways that lead through a variety of mechanisms to adverse effects (Chen and Eastmond, 1995B; Eastmond et al, 1987; Guy et al, 1991; Levay, 1992).

Understanding the relation between benzene metabolism and its mechanism(s) of toxicity is one part of the puzzle that must be solved if we are to move away from the routine default assumption that leads to linear extrapolation from high to low dose. A second part of this puzzle is to understand the relation between the observed biological effects of benzene metabolites and the mechanism(s) of carcinogenesis. The available information on these two parts of the puzzle does not always point in the same direction. For example, there is evidence suggesting that the metabolism of benzene to active intermediates saturates at higher doses which could mean that the dose response is supralinear. There is also evidence suggestive of aneuploidy being an important mechanism of benzene carcinogenesis, and it has been argued that such gross chromosome damage requires multiple "hits" indicating that the dose response to lower benzene levels is sublinear. There are counter arguments to each of the above.

Risk assessors have attempted to tease the biology out of the epidemiological findings. For example, Crump (1994) using a weighted exposure approach has calculated the apparent latency period for benzene leukemogenesis from the pliofilm cohort database and has inferred possible biological explanations for why his calculations result in a longer latency period for leukemia than was observed in radiation-exposed atom bomb survivors. Inferring biology from epidemiology can be useful for hypothesis generation but needs to be approached cautiously as a basis for risk assessment.

Current advances in molecular biology, including studies using these techniques in benzene-exposed humans and animals, provide much promise for the eventual unraveling of the mechanisms of

benzene hematotoxicity and leukemogenesis (Chen and Eastmand, 1995A; Rothman et al, 1995; Xu et al, 1998; Irons, 2000; Laskin, 2000; Mani et al, 1999; Smith and Rothman, 2000). But at the present time it is difficult to observe a clear pattern, or even a clear directional signal, that would permit a generally accepted biological basis for other than a classic linear model of benzene leukemogenesis.

Risk Assessment for Hematological Neoplasms Caused by Benzene.

The most recent EPA update on benzene (EPA, 1997) derives two risk estimates from the pliofilm cohort: a lifetime leukemia risk at 1ppm (3.2 mg/m^3) of 1.8×10^{-2} using an additive risk model, and 4.1×10^{-2} using a relative risk model. Both are based on linear low dose assumptions. These are little changed from previous EPA risk estimates of 2.6×10^{-2}, based primarily on the geometric mean of four maximum likelihood risk estimates (EPA, 1985) or of an even earlier risk estimate of 2.2×10^{-2} risk at 1ppm (3.2 mg/m^3) (Goldstein, 1985). The EPA (1997) NCEA review of different approaches based on the pliofilm data that use linear assumptions states that the risk at 1ppm (3.2 mg/m^3) ranges from 4.7×10^{-3} to 2.5×10^{-2}. Assuming low dose linear extrapolation this translates into a risk of 47-250 in a million for a 70 year lifetime exposure to 10 ppb benzene (3.2 mg/m^3), a reasonable upper bound for a community exposure level. Of note is that there is a reasonable similarity between benzene risk assessments derived from the human and animal cancer data (Goldstein, 1985).

There are three areas of uncertainty that are particularly pertinent to debates concerning the appropriate risk of benzene-induced cancers: (1) the extent of benzene exposure of workers in cohorts with an increased risk of ANLL, particularly the pliofilm cohort; (2) the appropriate shape of the dose-response curve for extrapolating the carcinogenic potential of much lower level benzene exposures; and (3) whether benzene also causes hematological cancers other than ANLL. The major uncertainty is the shape of the dose-response curve and particularly whether there is sufficient evidence to deviate from low-dose linearity.

(1) <u>Extent of benzene exposure in cohorts with an increased risk of ANLL</u>

One of the most thoroughly evaluated cohorts in the history of occupational epidemiology has been that of pliofilm workers in two Goodyear plants in Ohio. The increase in leukemia incidence among these workers put an end to any remaining doubt that benzene was a cause of ANLL (Infante et al, 1977). As benzene exposure levels had been reported within the then allowable 10 ppm TWA workplace standard, OSHA attempted to impose an Emergency Temporary Standard of 1 ppm, which was thrown out by the Federal court. During the formal rule making that followed, it became apparent that the pliofilm workers had in fact been exposed to benzene levels well above the standard. Identifying the actual exposure levels became particularly important to establishing the new workplace standard, and to establishing the leukemogenic risk of benzene. Rinsky and his colleagues at NIOSH performed what was then the most extensive retrospective cohort exposure assessment (Rinsky et al 1981). Not surprisingly, they were forced to make numerous assumptions as to past exposure levels. Particularly controversial was their assumption of what seemed to be relatively low levels of exposure during the World War II period. As pliofilm production was an

essential war industry, and a nationwide occupational health review made during this period indicated a rather cavalier use of benzene in such industries, it seems reasonable that exposure levels were significantly higher. Building on the work of Rinsky et al (1981), Crump and Allen (1984) Paustenbach et al (1992, 1993) and Paxton et al (1994A) performed extensive reanalyses of the exposure levels. Using the reported blood counts in these workers, my colleagues compared the Crump and Allen with the Rinsky analyses and found that the former more closely predicted the blood count variations (Kipen et al, 1988; Cody et al, 1993). But we pointed out that our findings were not relevant to the absolute exposure levels, only to the relative time variations.

The NIOSH researchers have vigorously defended their exposure assessment (Utterback and Rinsky, 1995). A more recent exposure analysis of the pliofilm cohort has been performed by Schnatter et al (1996) focusing on exposure levels of various worker subgroups in order to refine the risk estimates. However, EPA (1997) concluded that the various exposure assessments for the pliofilm cohort do not differ among themselves sufficiently to have a major impact on the 1985 estimate of risk based upon the epidemiologic data alone. Note that the debate about benzene exposure levels also has implications to mechanistic issues concerning dose rate and linearity.

Recent studies in China by scientists from the Chinese Academy of Preventive Medicine and the US National Cancer Institute have provided another data base from which one can attempt to relate an elevated risk of ANNL to workplace benzene exposure levels (Yin et al, 1987A, B, 1996A, B; Zhang et al, 1996; Rothman et al, 1995, 96; Hayes et al, 1997). The number of leukemia deaths is appreciably higher than that for the pliofilm cohort. A reconstructed exposure estimate for much of the cohort has been reported (Dosemici et al, 1994). While a very useful exercise, the inherent uncertainties in this dose reconstruction are already leading to controversy (Wong, 1998, 1999).

Preliminary review suggests that the resulting dose response estimates will be in the similar range of the leukemia dose response estimates for the pliofilm workers. However, it is still possible that ongoing prospective and retrospective studies of these heavily exposed workers will lead to more refined estimates of dose response patterns. Of perhaps greater importance to the issue of low dose linearity is the mechanistic information that may be obtained from study of these benzene-exposed workers.

Understanding the dose portion of the benzene dose-response relationship requires knowledge of the specific workplaces. For most industrial settings there tends to be large variations in the extent of individual exposure which is often not apparent from usual industrial hygiene measurements. Workers may be in a part of the refinery or chemical factory that is particularly prone to have a leaking valve. Or there may be individual habits that should be prevented, such as using benzene to wash off grease and grime from hands or clothes. Smaller and unregulated workplaces, which seem to characterize the Chinese experience, may well have a larger degree of individual variation. This variation is important, particularly for establishing leukemia risk, because fortunately only a small percentage of even a highly exposed workforce develops ANNL. Area benzene measurements may not reflect the actual exposure of those relatively few individuals, raising questions as to the validity of risk assessments based on such measurements, particularly in workplaces with highly variable exposure conditions.

(2) The linearity of the dose response curve for leukemogenesis

Extrapolation of benzene carcinogenesis from the benzene levels observed in the pliofilm or Chinese studies to the three or so orders of magnitude lower levels pertinent to community exposure levels has been highly controversial. There have been numerous analyses that have argued that these data, or others, provide evidence of a non-linear, sublinear or threshold for benzene leukemogenesis (see for example Paxton, et al, 1994B: Cox, 1996; Schnatter et al, 1996; Wong and Raabe, 1995) that would lead to a substantial decrease in the estimated risk for the lower level exposures relevant to community benzene exposures. EPA (1997) has claimed that more than 100 risk estimates have been presented, and that they vary by 6 orders of magnitude at 1 ppb. The key issue is whether the extrapolation is assumed to be linear or non-linear. In essence, EPA has defended linear extrapolation as the preferred approach unless there is adequate biological evidence supporting a different dose response relationship.

The most extensively analyzed cohort of benzene exposed workers to date has been that of the pliofilm workers (Infante et al, 1977; Rinsky et al, 1981, 1987). A key issue is that with only 9 cases of leukemia in the Rinsky, 1987 follow-up, versus 2.66 expected, there is very little stability in any of the analyses. This follow up study may not have been warranted given the relatively short latency period for ANLL as compared to solid tumors and the higher benzene exposures in the past. In essence, additional follow up may dilute out the true effect and only add cases that are unrelated to benzene exposure, thereby obfuscating the dose response issues even further.

Hayes et al (1997) did an extensive analysis of hematologic neoplasms in Chinese workers, reporting on a cohort of 74,828 benzene-exposed and 35,805 unexposed workers. Their key finding was that for workers historically exposed to benzene at levels of 10 ppm (32 mg/m^3) or less there was an elevated relative risk for all hematological tumors combined of 2.2 (95% CI 1.1-4.2). For ANLL and myelodysplasia the RR was 3.2 (95% CI 1.0-10.1). When the exposure levels were consistently 25 ppm or more, the RR for ANLL and myelodysplasia was 7.1 (95% CI 1.1-15.9). Risk for non-Hodgkin's lymphoma, an unusual tumor in China, was also significantly increased. The authors cautiously note that the dose response curve for benzene-induced cancer from their study tended to flatten out suggesting a supralinear curve. The cohort was also reported upon with slightly different numbers (Yin et al, 1996B). This does response estimation has been criticized by Wong (1998, 1999) and by Wong and Raabe (2000).

The Health Council of the Netherlands reviewed benzene risk in 1987 and again in 1997 (Health Council, 1997). In 1987 the conclusion was that benzene was a human carcinogen and that it worked through a genotoxic mechanism. It was considered uncertain as to whether the mechanism of action was stochastic or non-stochastic, i.e. without or with a threshold. A linear extrapolation was chosen as it was deemed to be the more cautious approach. However, the Health Council believed that a simple linear extrapolation was not warranted as it would produce "excessively low" results that would be "overly safe". Accordingly they chose a factor of 100 higher than would otherwise result from a linear extrapolation to a one in one million lifetime risk. This resulted in a recommended exposure limit of 12 ug/m^3 of benzene in outdoor air.

Their more recent evaluation used a circuitous route to confirm the previously recommended level. The Health Council's benzene committee again stated itself as being uncertain as to whether benzene has a stochastic or non-stochastic mechanism of action. However, they were impressed by a study of 208,000 petrochemical employees said to have an average exposure to 0.7 mg/m^3 benzene which they interpret as showing no increase in ANLL (Wong and Raabe, 1995). They extrapolated this as being equivalent to 35ug/m^3 lifetime to the general population. They further concluded that this supported their earlier view that the exposure-response curve will be sublinear rather than linear. As there was still uncertainty as to the exact extrapolation technique they left the 12ug/m^3 recommendation intact as a one in one million risk.

(3) Does benzene cause hematological neoplasms other than ANLL?

One of the limitations in studying the effects of benzene in laboratory animals has been the difficulty in developing an animal model of benzene-induced ANLL. However, studies in laboratory animals have clearly demonstrated that benzene causes hematological neoplasms other than ANLL as well as non-hematological neoplasms (Maltoni, 1983; NTP, 1984; Snyder et al, 1982). This has naturally raised the question of whether benzene can cause cancers other than ANLL in humans (Savitz and Andrews, 1997; Goldstein, 1990; Goldstein and Witz, 2000). I believe that the answer is most likely yes, but still scientifically unproven, for a variety of hematological tumors including non-Hodgkins lymphoma (NHL), multiple myeloma and acute lymphatic leukemia (ALL).

In each of these three tumors derived from lymphocytic cells there is some epidemiological support, although controversial, as well as a strong element of biological plausibility. Lymphocytic cells are particularly at risk to benzene toxicity, the lymphocyte count decreasing even more rapidly than does the granulocytic count. Further, chromosomal effects are readily observed in the lymphocytes of humans and animals with significant benzene exposure. And longer term exposures to benzene causes lymphomas in laboratory animals.

This is not the place to enter into the details of the controversy concerning the epidemiology. Briefly, Wong and Raabe and their colleagues have recently published two large meta analyses in which they report no increased incidence of either multiple myeloma or of NHL (Bergsagel et al, 1999; Wong and Raabe, 2000). Both are seriously flawed by the fact that the populations under study do not appear to have had a statistically significant increased incidence of ANLL, reflecting the fact that benzene exposure for most workers in the petroleum industry is relatively well controlled and that many workers in these cohorts are at little risk of benzene exposure (Goldstein and Shalat, 2000; Bergsagel et al, 2000). It is unreasonable to ask the question of whether benzene can cause NHL or multiple myeloma in a cohort in which there is not a clear signal of benzene induced ANLL. The fallacy is similar to asking whether cigarette smoking can cause NHL in a large cohort whose level of cigarette smoking is too low to cause a statistically significant increase in risk of lung cancer.

An additional problem with their approach is exemplified by the findings of Rushton and Alderson (1981). Their nested case control study of leukemia in British petroleum workers showed a positive association between workplace benzene exposure and leukemia despite an overall SMR for leukemia

of 0.95. Wong et al (1999) have published a nested case control study of leukemia, acute myelogenous leukemia, multiple myeloma and kidney cancer in a cohort of petroleum workers exposed to gasoline. As they did not find an increased risk of acute myelogenous leukemia or of all leukemias in relation to benzene exposure, their negative findings for kidney cancer and multiple myeloma are simply not relevant to the issue of whether benzene can cause these latter two cancers. ALL is primarily a disease of children. While children are exposed to community sources of benzene, their absence from the workforce precludes usual epidemiological approaches to the question of whether benzene can cause ALL. About the most that we can reasonably conclude at present is that it is highly unlikely that the potency of benzene in producing ANNL is exceeded by its potency in producing any other human cancer.

A major issue in all of the extrapolation approaches from the pliofilm cohort is the lack of sensitivity due to the relatively small numbers involved. These small numbers also impact on the usual epidemiological approaches to determine if causality exists. For example, the four cases of multiple myeloma observed in the initial pliofilm study (Rinsky, 1981) were not preferentially observed in the more highly exposed work categories. But with only four myeloma cases, with one expected, it is hard to put much credence in the lack of a dose-related distribution. Similarly, Wong and Raabe (2000) have dismissed the finding of Consonni et al (1999) in which five cases of NHL were observed (2.12 expected) because of a lack of a statistically significant upward trend.

To summarize the above, in my judgment it is very likely but scientifically unproven that benzene causes hematological neoplasms other than NHL. A reasonable assumption is that this might lead to a doubling of the overall cancer risk.

Risk assessment for non-cancer hematological effects

There is no question that benzene causes hematological effects other than cancer. High level workplace exposures to benzene usually lead to more deaths from aplastic anemia than from ANLL. Further, in large well studied cohorts in which there have been cases of aplastic anemia, there are usually many more cases of pancytopenia with all degree of gradation from very mild to highly significant. Clinical manifestations other than the laboratory findings include symptoms due to anemia, an increased risk of infection due to a low white blood count, and an increased risk of hemorrhage due to a low platelet count. In attempting to estimate the health costs, it should be noted that there is a wide gap between the lower end of the statistically normal range of blood count values and the much lower blood counts that are required for symptoms or for overt clinically recognizable disease consequences that could be readily used for economic analysis. An individual with a mild to moderate benzene-induced pancytopenia will likely be clinically unrecognizable unless he or she happens to have routine blood counts.

For the purposes of the present exercise I will briefly attempt to distinguish among three levels of benzene induced non-cancerous effect: 1) the exposure level that will produce a clinically recognizable endpoint such as symptomatic anemia, infection or hemorrhage; (2) the exposure level that will produce a lowering of blood count(s) below normal levels; and (3) the level of benzene that might have any detectable hematological effects.

(1) Symptomatic effects: Such effects undoubtedly require benzene exposures well above the 10 ppm (32 mg/m^3) TWA workplace standard in effect for a few decades in the United States and elsewhere. Literally millions of workers were subjected to routine blood counts on a quarterly to annual basis. The reason the OSHA standard was decreased to its present 1 ppm level was solely because of cancer concerns, not because the higher standard was leading to non-cancer hematological disease. Recent data from China describe clinical aplastic anemia in factories with exposure levels said to range from 93-1156 mg/m^3 (Yin et al, 1987b). A not unreasonable assumption is that clinically overt symptoms will not occur as a result of long term benzene exposure to levels at the workplace below 100 mg/m^3, or perhaps much higher.

(2) Blood count(s) below the normal range: There are a number of studies evaluating blood counts in workers exposed to reasonably well defined levels of benzene, although in each study there is some grounds for uncertainty as to whether the measured benzene levels are pertinent to the specific individuals with low blood counts. In most cases the availability of blood count data is related to surveillance of benzene-exposed workers. Complicating interpretation of these blood count data is the fact that there are many reasons for variations in blood counts below the statistically normal value, some related to normal biological variation, some to laboratory variation, and some to the many other causes of low blood counts for reasons as diverse as viral infections and alcoholism.

Perhaps the most extensive study of workers exposed to benzene is that of Yin et al (1987b) who found 2,676 cases of benzene poisoning, defined as a white blood count less than 4,000/mm^3, in a review of over 500,000 benzene-exposed workers in China. The geometric mean concentration in 50,255 workplaces was 18.1 mg/m^3, and 64.6% of the workplaces had less than 40 mg/m^3. From their review of the data the authors conclude that cases of benzene poisoning may occur even in factories with less than 40 mg/m^3 benzene.

Gross chromosomal abnormalities in association with overt benzene hematotoxicity were originally reported by Forni et al (1971; see also Forni, 1996). More recent findings of chromosomal abnormalities using fluorescent in situ hybridization technique have been reported in Chinese workers with benzene exposure above 31 ppm (99 mg/m^3; Zhang et al, 1996).

(3) Any detectable hematological effects: Sensitive indicators of bone marrow toxicity have been explored in animal studies aimed primarily at determining the mechanism of benzene hematotoxicity. Mice are more sensitive to rats. Green et al (1981) looked at specific progenitor bone marrow cells in mice and reported effects at inhalation exposure levels of 9.9 ppm (32 mg/m^3), but not 1.1 ppm (3.5 mg/m^3) benzene, 6 hours per day for 5 days. Farris et al (1997) evaluated similar endpoints in mice. They found effects at 100 and 200 ppm (320 and 640 mg/m^3), 6 hrs a day for up to 8 weeks, but not at 1,5, and 10 ppm (3.2, 16 and 32 mg/m^3). Cytogenetic endpoints also have been evaluated in laboratory animals.

There are a number of worker studies that have reported statistically significant changes in hematological endpoints at relatively low benzene exposure levels. Ward et al (1996) reported on the blood counts of the pliofilm workers and suggested that there may be no threshold for the hematologic effects of benzene which may occur even at levels less than 5 ppm (16 mg/m^3). On the

other hand, Tsai et al (1998), based upon the lack of evidence of effects in hematological monitoring results from 2475 employees at a petrochemical complex, questioned the need for this form of surveillance. Khuder et al (1999) reported on a group of 105 petroleum workers exposed to 0.14 -2.08 ppm (0.45 - 6.6 mg/m^3) benzene who over time had small but statistically significant falls in certain blood counts. However, there were problems with this study, including a decrease in the red cell mean corpuscular volume, a finding contrary to what is observed in benzene toxicity (Goldstein and Cody, 2000). Nilsson et al (1996) reported findings suggestive of genotoxic effects in men occupationally exposed to relatively low levels of benzene in the range of 0.1 ppm (0.3 mg/m^3), but there were other exposures as well. Multiple exposures also is a confounding factor in the report of Carere et al (1995) of cytogenetic changes in Rome gasoline station attendants. There were also inconsistencies in relation to benzene exposure levels.

In summary, there is no convincing evidence of any non-neoplastic hematological effects at benzene levels in the range of current community air pollution levels.

Susceptibility issues

There is ample indirect evidence, as well as some direct evidence, of differences in susceptibility to the hematological effects of benzene among individuals. Women are believed to be more susceptible than men due to an average higher body fat leading to more benzene storage. There are genetic polymorphisms governing the activity of many of the known steps in the benzene metabolic pathway. One of the more intriguing recent findings in the field of genetic polymorphisms is the observation by Rothman et al (1997) that the risk of decreased blood counts among Chinese workers exposed to benzene increased seven-fold if the workers had two different phenotypic variations that led on the one hand to increase the rate at which initial benzene metabolism produced hydroxylated intermediates and on the other hand slowed the rate of detoxification of these metabolites. Workers with only one of these variants had approximately a doubling of risk. There is also the suggestion in the older literature that individuals with thalassemia were at increased risk of benzene toxicity, an observation that is perhaps generalizable to any groups with increased bone marrow precursors due to inherited anemias, e.g., sickle cell disease. Much of this work needs to be followed up before it can be used in economic analyses.

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